Remarks

Claim 52 has been cancelled. Claim 53 has been amended to put in independent form. Claims 54-55, 57-60 and 62-63 have been amended so as to depend from now independent claim 53. No new matter is added by virtue of the amendments contained herein.

Applicants appreciate Examiner Jagoe's time and consideration during a telephone interview July 27, 2006. During the interview, the Office Action mailed June 22, 2006 was discussed, including the rejections under 35 USC §112, as well as the Examiner's view of the present rejections. It is believed the amendments and remarks contained herein address the present Examiner's concerns under 35 USC §112.

Claims 52 and 55-63 were rejected under 35 USC §112, first paragraph. Applicants respectfully traverse the rejections.

The Examiner maintained while the specification is enabling for treating malaria caused by Plasmodium parasite, P. falciparum with hydroxydiphenyl ether compounds, it does not reasonably provide enablement for other Plasmodium parasites that cause malaria, or the addition of other antimalarial agents with the hydroxyphenyl ethers. Further, the Examiner asserted the specification lacks written description of the chemical structure of the hydroxydiphenyl ether other than those disclosed in claims 53 and 54.

Applicant thanks Examiner Jagoe for careful consideration of the present case. During the interview, the rejections issued in the Communication mailed June 22, 2006 were discussed for clarification. Following discussion with Examiner Jagoe, Applicants have cancelled Claim 52 and amended Claim 53 to be in independent form. Additional amendments have been incorporated so as to correct dependency of subsequent dependent claims accordingly. No new matter is added by virtue of these amendments. During the interview the claim scope was discussed, and Examiner Jagoe indicated such amendment, apart from any art arising from a search of the genus of claim 53, would render the claim allowable. Furthermore, the Examiner confirmed dependent claims including additional antimalarial agents would be considered allowable if dependent upon an allowable base claim.

Furthermore, in discussing the rejection under 35 USC §112 relating to enablement of treatment of malaria caused by additional species of *Plasmodium*, Applicants appreciate the Examiner's indication that the claims would satisfy the enablement requirement if a submission supporting the role fatty acid synthesis among malaria parasites were provided. In support of such enabling disclosure, Applicants submit herewith a review web-published review article describing the biochemistry of plasmodium, supporting that type II fatty acid synthesis is a conserved critical pathway in the apicoplast of *plasmodium*. See Biochemistry of Plasmodium. Crawford, M., http://www.tulane.edu/~wiser/malaria/Summary.html, at "Fatty Acids and Lipids" and "The Apicoplast" sections.

In addition, a recent article (Waller et al.) and and abstract (Lu et al.) discussing the importance of antimalarial compounds which target type II fatty acid biosynthetic pathways are submitted herewith, further supporting the conserved role of type II fatty acid biosynthesis in malaria parasites.

Furthermore, the target of compounds of the invention has been found to be enoyl-ACP reductase, an enzyme which function and sequence is conserved throughout bacteria, including *Plasmodium* species. For example, alignment of Genbank sequences of *Plasmodium sp.* (*P. berghei, P. yoelii yoelii, P. chabaudi, P. falciparum, P. vivax, and P. knowlesi*) Enoyl ACP reductase proteins demonstrates conserved protein sequences among the species. In fact, each of the critical residues found to be involved in interaction with triclosan and other inhibitors (e.g., A217, N218, V222, Y267, Y277, M281, P314, K285, F368, and I 369 in *P. falciparum*) are conserved identical residues among each of these species. A multiple alignment of these sequences is enclosed, with each of the conserved identical residues boxed.

Copies of references identifying the structural interactions (Perozzo, et al.; Kapoor et al., Kapoor et al.), as well as each of the protein database citations for the sequences are also submitted herewith. Each of the references cited herein is submitted in IDS Form 8B, in conjunction with copies of the references. It is believed no fee is due in connection with this submission. Entry and consideration of the references cited is requested.

It is believed the present amendments render any rejection under 35 USC §112 moot. In view of the amendments and remarks presented herein, Applicant respectfully submits that the case is in condition for allowance. A Notice to that effect is earnestly requested.

If, at any time, it appears that a phone discussion would be helpful, the undersigned would greatly appreciate the opportunity to discuss such issues at the Examiner's convenience. The undersigned can be contacted at (617) 248-5000 or (617) 248-4831 (direct dial).

It is believed no fee is due in connection with this submission, as this response is filed in advance of the three month period for response. However, in the event any fees are due, please charge any fees associated with this filing, or apply any credits, to our Deposit Account No. 03-1721.

Respectfully submitted,

Kerri Pollard Schray, Ph.D.
Registration Number 47,066

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Dated: September 12, 2006

4110978_1.DOC

APPENDIX
SEQUENCE ALIGNMENTS

CLUSTAL W (1.83) Multiple Sequence Alignments

Sequence type explicitly set to Protein
Sequence format is Pearson
Sequence 1: AAK38273[P_falciparum] 432 aa
Sequence 2: AAK25802[P_falciparum] 431 aa
Sequence 3: AAK38274_[P_falciparum] 432 aa
Sequence 4: AAR00332_[P_berghei] 396 aa
Sequence 5: EAA19619_[P_yoelii_yoelii] 404 aa
Sequence 6: AAR00334_[P_vivax] 401 aa
Sequence 7: AAR00333_[P_knowlesi] 413 aa
Sequence 8: CAH74886_[P_chabaudi] 356 aa
Start of Pairwise alignments
Aligning...

Sequences (1:2) Aligned. Score: 99.3039
Sequences (1:3) Aligned. Score: 98.3796
Sequences (1:4) Aligned. Score: 62.8788
Sequences (1:5) Aligned. Score: 61.3861
Sequences (1:6) Aligned. Score: 58.8529
Sequences (1:7) Aligned. Score: 59.322
Sequences (1:8) Aligned. Score: 68.2584
Sequences (2:2) Aligned. Score: 100
Sequences (2:3) Aligned. Score: 97.6798
Sequences (2:4) Aligned. Score: 61.6162
Sequences (2:5) Aligned. Score: 59.6535
Sequences (2:6) Aligned. Score: 57.8554
Sequences (2:7) Aligned. Score: 58.3535
Sequences (2:8) Aligned. Score: 66.8539
Sequences (3:2) Aligned. Score: 97.6798
Sequences (3:3) Aligned. Score: 100
Sequences (3:4) Aligned. Score: 62.6263
Sequences (3:5) Aligned. Score: 61.3861
Sequences (3:6) Aligned. Score: 58.8529
Sequences (3:7) Aligned. Score: 59.0799
Sequences (3:8) Aligned. Score: 68.2584
Sequences (4:2) Aligned. Score: 61.6162
Sequences (4:3) Aligned. Score: 62.6263
Sequences (4:4) Aligned. Score: 100
Sequences (4:5) Aligned. Score: 93.9394
Sequences (4:6) Aligned. Score: 60.6061
Sequences (4:7) Aligned. Score: 61.8687
Sequences (4:8) Aligned. Score: 92.6966
Sequences (5:2) Aligned. Score: 59.6535
Sequences (5:3) Aligned. Score: 61.3861
Sequences (5:4) Aligned. Score: 93.9394
Sequences (5:5) Aligned. Score: 100
Sequences (5:6) Aligned. Score: 60.3491
Sequences (5:7) Aligned. Score: 60.396
Sequences (5:8) Aligned. Score: 92.1348
Sequences (6:2) Aligned. Score: 57.8554
Sequences (6:3) Aligned. Score: 58.8529
Sequences (6:4) Aligned. Score: 60.6061
Sequences (6:5) Aligned. Score: 60.3491
Sequences (6:6) Aligned. Score: 100
Sequences (6:7) Aligned. Score: 85.0374
Sequences (6:8) Aligned. Score: 66.8539
Sequences (7:2) Aligned. Score: 58.3535
Sequences (7:3) Aligned. Score: 59.0799
Sequences (7:4) Aligned. Score: 61.8687
Sequences (7:5) Aligned. Score: 60.396
Sequences (7:6) Aligned. Score: 85.0374
Sequences (7:7) Aligned. Score: 100
Sequences (7:8) Aligned. Score: 66.2921
Sequences (8:2) Aligned. Score: 66.8539
Sequences (8:3) Aligned. Score: 68.2584
Sequences (8:4) Aligned. Score: 92.6966
Sequences (8:5) Aligned. Score: 92.1348

```
Sequences (8:6) Aligned. Score: 66.8539
Sequences (8:7) Aligned. Score: 66.2921
Sequences (8:8) Aligned. Score: 100
Guide tree       file created:   [clustalw.dnd]
Start of Multiple Alignment
There are 7 groups
Aligning...
Group 1: Sequences:   2      Score:6254
Group 2: Sequences:   3      Score:5591
Group 3: Sequences:   2      Score:7042
Group 4: Sequences:   3      Score:7037
Group 5: Sequences:   6      Score:5552
Group 6: Sequences:   2      Score:6040
Group 7: Sequences:   8      Score:5370
Alignment Score 46687
CLUSTAL-Alignment file created  [clustalw.aln]
```

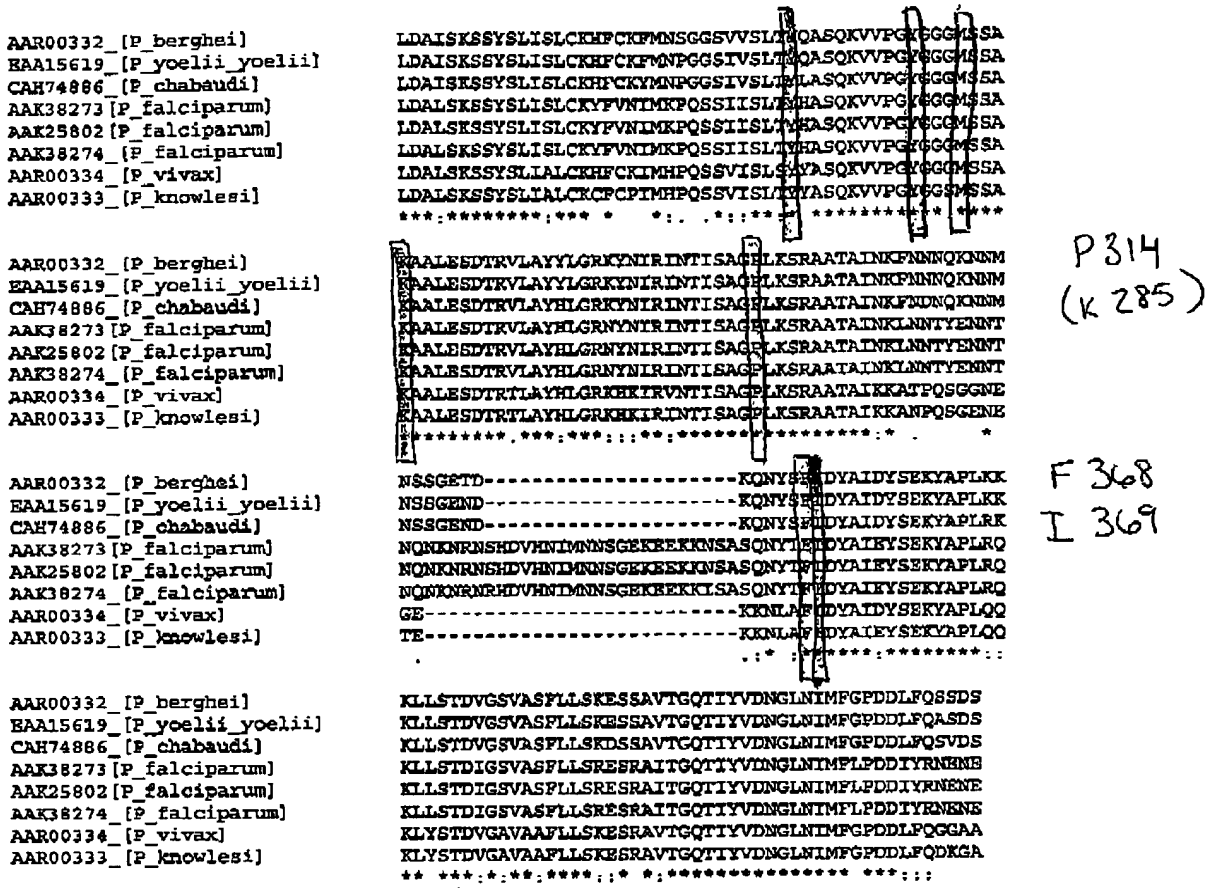
clustalw.aln

CLUSTAL W (1.83) multiple sequence alignment

```
AAR00332_[P_berghei]            ------------MYKKLIVFLTILIFNYLKITCFTNNGYEKKTPSSLRMN
EAA15619_[P_yoelii_yoelii]      -----------MYKKVILFLIISIFNYLKITCFTNTGYEKKTYPSLRMN
CAH74886_[P_chabaudi]           ------------------------------------------------MN
AAK38273_[P_falciparum]         ------------MNKISQRLLFLFLHFYTIVCFIQN-NTQKTFHNVLHN
AAK25802_[P_falciparum]         ------------MNKISQRLLFLFLHFYTIVCFIQN-NTQKTFHNVLHN
AAK38274_[P_falciparum]         ------------MNKISQRLLFLFLHFYTIVCFIQN-NTQKTFHNVLQN
AAR00334_[P_vivax]              -----------MHVRRVVQLATLLLYIASVSAMLRSALKGGGQPKWEIE
AAR00333_[P_knowlesi]           MEKIYSGGSRGRMHTGRLVHLAALLLWIAAVSGILRNGTKGGVQPKWAIE
                                                                               :

AAR00332_[P_berghei]            KENYWKNKILRKKKNENNLRINVESNQNDKIDNIKNKNENE----------
EAA15619_[P_yoelii_yoelii]      KENYWKNKILRKNKNENNLRINVGSSQNDIIENIKNGSENGSVSGSESG-
CAH74886_[P_chabaudi]           NQNYWKNKILRKIKNENNLRINVESNQSDKIEDIKNE------------
AAK38273_[P_falciparum]         EQIRGKEKAFYRKEKRENIFIGNKMKHLNNMNNTHNNNHYMEKEEQDASN
AAK25802_[P_falciparum]         EQIRGKEKAFYRKEKRENIFIGNKMKHLNNMNNTHNNNHYMEKEEQDASN
AAK38274_[P_falciparum]         EQIRGKEKAFYRKEKRENIFIGNKMKHVHNMNNTHNNNHYMEKEEQDASN
AAR00334_[P_vivax]              RRGNSREMQFITSKAIKGVAHKRKISQHSSPAEHMVSEQSGQAEGLNGKG
AAR00333_[P_knowlesi]           KRGNSREMQFMVSKVIKGVAQNRKISQHLSHSEKMLSEQNGQGEETNKKG
                                ..   :: :   :  :.:      .:     :

AAR00332_[P_berghei]            ----------NEICFIAGVGDSNGYGWGIAKELSKRNVKVIFGVWPPVYN
EAA15619_[P_yoelii_yoelii]      ----------SEICFIAGVGDSNGYGWGIAKELSKRNVKVIFGVWPPVYN
CAH74886_[P_chabaudi]           ----------NEICFIAGVGDSNGYGWGIAKELSKRNVKVIFGVWPPVYN
AAK38273_[P_falciparum]         IYKIKEENKNEDICFIAGIGDTNGYGWGIAKELSKRNVKIIFGIWPPVYN
AAK25802_[P_falciparum]         IYKIKEENKNEDICFIAGIGDTNGYGWGIAKELS-RNVKIIFGIWPPVYN
AAK38274_[P_falciparum]         INKIKEENKNEDICFIAGIGDTNGYGWGIAKELSKRNVKIIFGIWPPVYN
AAR00334_[P_vivax]              -------EPLGDICFIAGVGDTNGYGWGIAKELSKKNVKIILGVWPPVYN
AAR00333_[P_knowlesi]           -------ETLGDICFIAGVGDTNGYGWGIAKELSKKNVKVILGVWPPVYN
                                      :******:**:************ :***:*:*:******

AAR00332_[P_berghei]            IFIKNLESGKFDKDMIINNDNSKRMQILDVLPLDAGFDNYDDIDEDTKNN
EAA15619_[P_yoelii_yoelii]      IFIKNLESGKFDKDMIINNDNLKRMEILDVLPLDAGFDNYDDIDEDTKNN
CAH74886_[P_chabaudi]           IFIKNLESGKFDKDMIIDNDNSKRMEILDVLPFDAAFDNYDDIDEDTKNN
AAK38273_[P_falciparum]         IFMKNYKNGKFDNDMIIDKD--KKMNILDMLPFDASFDTANDIDEETKNN
AAK25802_[P_falciparum]         IFMKNYKNGKFDNDMIIDKD--KKMNILDMLPFDASFDTANDIDEETKNN
AAK38274_[P_falciparum]         IFMKNYKNGKFDNDMIIDKD--KKMNILDMLPFDASFDTANDIDEETKNN
AAR00334_[P_vivax]              IFMKNLQSGKFDSDMIIGEG--KKMSLLDILPFDAAFDSASDVDEETRKN
AAR00333_[P_knowlesi]           IFMKNLENGKFDNDMEIGEG--RKMDLLDILPFDAAFDSFNDIDEETRKN
                                **:** ..****.** *.:.  ::*::**:**:**.**.  .*:**:*::*

AAR00332_[P_berghei]            KRYNNLKNYSIEEVANLIYNKYGKISMLVHSLANGREVQKSLLDTSRDGY
EAA15619_[P_yoelii_yoelii]      KRYNNLKNYSIEEVANLIYNKYGKISMLVHSLANGREVQKSLLDTSRDGY
CAH74886_[P_chabaudi]           KRYNNLKNYSIEETANLVYNKYGKISMLVHSLANGREVQKNLLDTSRDGY
AAK38273_[P_falciparum]         KRYNMLQNYTIEDVANLIHQKYGKINMLVHSLANAKEVQKDLLNTSRKGY
AAK25802_[P_falciparum]         KRYNMLQNYTIEDVANLIHQKYGKINMLVHSLANAKEVQKDLLNTSRKGY
AAK38274_[P_falciparum]         KRYNMLQNYTIEDVANLIHQKYGKINMLVHSLANAKEVQKDLLNTSRKGY
AAR00334_[P_vivax]              KRYASLDSYSIEEVANLVYKKYGKINMLVHSLANGREVERSLLETSRGGY
AAR00333_[P_knowlesi]           KRYANLESYSIEEVANLIYKKYGKINMLVHSLANGREVEKSLLDTSRNGY
                                *** *..*:**:.***:::******.********.:*:::.**:*** **
```

A27
N218
V222.

Y267 Y277 M128

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clustalw.dnd

(
(
AAK38273[P_falciparum]:-0.00131,
AAK25802[P_falciparum]:0.00827)
:0.00895,
AAK38274_[P_falciparum]:0.00727,
(
(
(
AAR00332_[P_berghei]:0.02418,
EAA15619_[P_yoelii_yoelii]:0.03643)
:0.03808,
CAH74886_[P_chabaudi]:0.00746)
:0.11376,
(
AAR00334_[P_vivax]:0.07643,
AAR00333_[P_knowlesi]:0.07319)
:0.13660)
:0.19068);
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